## *Remarks*

Reconsideration of this Application is respectfully requested.

Applicant respectfully requests that this Amendment and Reply under 37 C.F.R. § 1.111 be entered by the Examiner.

Upon entry of the foregoing amendment, claims 10-15 and 17-52 are pending in the application, with claims 10 and 52 being the independent claims. Claims 10-15 and 52 are sought to be amended and claim 15 is sought to be canceled without prejudice or disclaimer of the subject matter therein. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Claims 10 and 52 have been amended by deleting the terms "preventing" and "prevent." Claims 10-15 and 52 have been also amended by replacing the term "chronic pain" with --neuropathic pain--. Claim 12 has been amended by deleting the term "neuropathic pain" as redundant and the terms "inflammatory pain" and "postoperative pain" to make claim 12 properly dependent from claim 10. Claim 13 has been amended by deleting the terms "inflammatory pain", "postoperative pain", "osteoarthritis pain associated with metastatic cancer", "gout" and "burn pain" to make claim 13 properly dependent from claim 10. Support for the amendments to claims 10-15 and 52 can be found in the specification and claims as originally filed. Applicant reserves the right to file one or more divisional applications directed to the subject matter of canceled claim 15 and the subject matter deleted from claims 10-15 and 52.

Based on the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

***Rejection Under 35 U.S.C. § 112, first paragraph***

The Examiner has rejected claims 10-21, 34-45 and 50-52 under 35 U.S.C. § 112, first paragraph, as allegedly not enabling any person skilled in the art to which it pertains, or with which it is most nearly connected to, to practice the invention commensurate in scope with these claims. Applicant respectfully traverses this rejection.

Specifically, the Examiner states that "the specification, while being enabling for treating or ameliorating the specific chronic pain such as neuropathic pain, does not reasonably provide enablement for treating or preventing "chronic pain"."

Applicant respectfully disagrees. However, in order to expedite the prosecution of the pending claims, Applicant has amended claims 1 and 52 by deleting the terms "preventing" and "prevent." Applicant submits that the Examiner's rejection with regard to preventing "chronic pain" is rendered moot.

With regard to treating "chronic pain", the Examiner alleges that one of ordinary skill in the art would have not known how to treat inflammatory pain, postoperative pain, cancer pain, phantom limb pain and idiopathic pain without undue experimentation, because the specification provides a study showing the coadministration Co 102862 and gabapentin in the Chung model of neuropathic rats and neuropathic pain differs from inflammatory pain, postoperative pain, cancer pain, phantom limb pain and idiopathic pain (page 6, line 17 through page 7, line 2 of the Office Action).

Applicant respectfully disagrees. Applicant submits that idiopathic pain, including phantom limb pain, is a neuropathic pain disorder. Support for this can be found at page 7, lines 1-5, of the original specification describing that neuropathic pain

includes pain from limb amputation and that phantom limb pain is idiopathic pain. Further, Rosenberg *at al.*, cited by the Examiner, describes a study on the effect of gabapentin on neuropathic pain. The reference includes phantom limb pain into neuropathic pain (see page 252, right col., lines 10-13). Further, Applicant respectfully submits that a person skilled in the art would know that chronic pain due to cancer may result from tumor growth compression of adjacent nerves, brain or spinal cord and, thus, is cancer-related neuropathic pain. In addition, cancer treatments, including chemotherapy and radiation therapy, can also cause nerve injury resulting in neuropathic pain.

Claims 10-15 and 52 have been amended by replacing the term "chronic pain" with --neuropathic pain--. Claim 12 has been amended by deleting the terms "inflammatory pain" and "postoperative pain." Claim 13 has been amended by deleting the terms "inflammatory pain", "postoperative pain", "osteoarthritis pain associated with metastatic cancer", "gout" and "burn pain" to make claim 13 properly dependent from claim 10. It is respectfully submitted that one having ordinary skill in the art would have known how to treat neuropathic pain as claimed in claims 1 and 52 as amended, and the specific neuropathic pain disorders claimed in claims 12-15 as amended, in view of teaching in the specification without undue experimentation.

In view of the above, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, of claims 10-21, 34-45, and 50-52.

***Rejection Under 35 U.S.C. § 112, second paragraph***

The Examiner has rejected claim 17 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicant respectfully traverses this rejection.

The Examiner alleges that the term "substantially" is a relative term which renders the claim indefinite. Further, the Examiner argues that "[t]he term "substantially" is not defined by claim, the specification does not provide a standard for ascertaining what is meant by "substantially simultaneously", and one of ordinary skill in the art would not be reasonably apprised of the scope of the claimed invention." Applicant respectfully disagrees.

Applicant submits that the phrase "substantially simultaneously" is definite. The specification as filed at page 23 clearly provides a standard for the phrase "substantially simultaneously" as follows: "the sodium channel blockers, gabapentin and/or pregabalin are administered in sequence or at the same time so long as effective blood levels of the sodium channel blockers, gabapentin and pregabalin are achieved at the same time" (see page 23, lines 15-18 of the specification). Therefore, it is respectfully submitted that the term "substantially" does not render claim 17 indefinite. See also M.P.E.P. § 2173.05(b).

In view of the above, Applicant respectfully requests reconsideration and withdrawal of the rejection of claim 17 under 35 U.S.C. § 112, second paragraph.

***Rejection Under 35 U.S.C. § 103(a)***

Applicant acknowledges with appreciation that the Examiner has withdrawn the rejection of claims 10-21, 34-45, and 50-52 under 35 U.S.C. § 103(a) over Wang *et al.* (Published International Appl. No. WO 98/47869) ("Wang") in view of Bryans *et al.* (*Medicinal Research Reviews 19(2)*:149-177 (1999)), and further in view of Applicant's allegedly admitted prior art (page 3, line 10 through page 4, line 5 of the specification) and Singh (U.S. Patent No. 6,001,876).

The Examiner has rejected claims 10-21, 34-45, and 50-52 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Wang *et al.* (Published International Appl. No. WO 98/47869) ("Wang") in view of Rosenberg *et al. (The Clinical Journal of Pain 13*:251-255 (1997)) ("Rosenberg"), and further in view of Bueno *et al.* (U.S. patent No. 6,242,488 B1) ("Bueno") and Caruso *et al.* (U.S. Patent No. 6,187,338) ("Caruso"). Applicant respectfully traverses this rejection.

In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences *themselves* would have been obvious, but whether the claimed invention as a whole would have been obvious. *See* M.P.E.P. § 2141.02. Applicant respectfully submits that none of the claims 10-21, 34-45, or 50-52 is rendered obvious by the teachings of Wang, Rosenberg, Bueno, and Caruso, either alone or in combination.

The Examiner suggests that Wang differs from the claimed invention because (i) Wang fails to disclose the use of gabapentin in combination with a sodium channel blocker such as 4-(4'-fluorophenoxy)benzaldehyde semicarbazone (a/k/a Co 102862) in treating chronic pain, namely "trigeminal pain", "diabetic neuropathy" and "cancer pain";

(ii) the specific dosage amount of each active ingredient; and (iii) the delivery of said combination in various dosage forms including oral, parenteral, intravenous, intramuscular, intraperitoneal, transdermal or buccal forms and specific order of delivery of said combination. The Examiner alleges that "[t]o incorporate such teaching into the teaching of Wang, would have been obvious in view of Rosenberg who teaches the use of gabapentin for treating chronic pain such as neuropathic pain (e.g., neuralgia, diabetic neuropathy)."

The Examiner concludes:

> The . . . references in combination make clear that the sodium channel blocker (i.e., 4-(4'-fluorophenoxy)benzaldehyde semicarbazone) and gabapentin have been individually used for the treatment of chronic pain such as neuropathic pain. It is obvious to combine two compositions each of which is taught by prior art to be useful for same purpose; idea of combining them flows logically from their having been individually taught in the prior art. The combination of active ingredient with the same character is merely the additive effect of each individual component. *See In re Kerkhoven, 205 USPQ 1069 (CCPA 1980)* (Office Action at page 10, lines 12-18).

Applicant respectfully disagrees and submits that the facts in *Kerkhoven* and in the present invention are different. In *Kerkhoven*, the claimed invention was rejected as obvious because, according to the Examiner, the mere mixing of two compositions each taught for the same purpose was obvious in the absence of a showing of unexpected results. However, the present invention demonstrates unexpected results, *i.e.*, a

synergistic effect between the two co-administered components. In other words, the present invention shows an effect of the two co-administered compounds that is greater than what would have been expected from merely adding the effects of the two components administered individually. *See* Applicant's specification, Example 1, page 32, line 24 through 33, line 2, and Figure 1. Figure 1 shows that the withdrawal thresholds at the time 2 hours after administration of (i) the sodium channel blocker, 4-(4'-fluorophenoxy)benzaldehyde semicarbazone (i.e., Co 102862), (ii) gabapentin, and (iii) the combination of the two compounds are 10^0.30=2.00 gms, 10^0.62=4.17 gms and 10^0.96=9.12 gms, respectively. These calculations show the taking of the antilogarithm of Figure 1 ordinate values, which are reported as their $base_{10}$ logarithms.

If there was only an additive effect for the combination treatment, the expected withdrawal threshold for the combination treatment would be 2.00 gms + 4.17 gms = 6.17 gms. This would be significantly smaller than the actual reported value for the combination treatment of 9.12 gms and, thus, the combination treatment appears to show a synergistic effect.

In view of the above, the Applicant's specification as originally filed demonstrates experimental results that the tactile anti-allodynia effect of 4-(4'-fluorophenoxy)benzaldehyde semicarbazone (Co 102862) *p.o.* and gabapentin *s.c.* administered in combination is not merely additive of the two individual components, but rather is greater than the sum of the individual compound's effects. Therefore, Applicant respectfully submits that none of claims 10-21, 34-45, or 50-52 is rendered obvious by the teachings of Wang and Rosenberg, either alone or in combination.

The Examiner has supplied Bueno "to demonstrate the routine knowledge in preparing gabapentin in various dosage forms" and Caruso "to demonstrate the routine knowledge in art in determining the delivery of various neuropathic pain-alleviating active ingredients including gabapentin in combination by separate administration or coadministration in single dosage forms." Applicant respectfully submits that neither Bueno nor Caruso remedies the deficiencies of Wang and Rosenberg.

In the Reply filed May 15, 2006, Applicant brought to the Examiner's attention International Application Publication No. WO 03/020273 (hereafter "the '273 publication"), indicating that subsequent to the filing of the instant application, other groups working in the field also demonstrated a synergistic effect for combinations of gabapentin with other sodium channel blockers. The '273 publication demonstrates that gabapentin administered with any of several other sodium channel blockers, *i.e.*, (S)-(+)-2-[4-(2-fluorobenzyloxy)benzylamino]propanamide (NW-1029), (R)-(-)-2-[4-benzyloxybenzylamino]-3-phenyl-N-methylpropanamide (NW-1037), or (S)-(+)-2-[4-(3-fluorobenzyloxy)-benzylamino]-N-methyl-propanamide (NW-1043), is likely to provide a synergistic effect when administered for chronic pain. The '273 publication was cited as document AM5 in the First Supplemental Information Disclosure Statement filed May 15, 2006.

In view of all of the above remarks, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) of claims 10-21, 34-45, and 50-52.

## *Conclusion*

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn.

In view of the foregoing remarks, Applicant submits that the claimed invention is not rendered obvious in view of the prior art references cited against this application. Applicant therefore requests the entry of this Amendment and Reply, as well as the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Applicant believes that a full and complete reply has now been made to the outstanding Office Action and that, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided. Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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